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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/941,398	JOHN, CONSTANCE MARY	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-13,15-18 and 20-24* is/are pending in the application.

4a) Of the above claim(s) *23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,7-13, 15-18,20-22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *28 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 8/13/04.

Claims 2-6, 14, and 19 have been canceled.

Claims 1, 7-13, 15-18, and 20-24 remain pending.

Claim 23 stands withdrawn because it is drawn to nonelected species.

Claims 1, 7-13, 15-18 and 20-22, and 24 and the species of neurotrophins are under consideration.

This Action is NON-FINAL due to new grounds of rejection not necessitated by Applicant's amendments.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: It was not executed in accordance with either 37 CFR 1.66 or 1.68. The oath is unsigned.

At page 15 of the response received 8/13/04, Applicant indicated that a signed oath was enclosed with the response. The PTO failed to find this document and scan it into the electronic file. The Examiner appreciates Applicant's efforts in faxing a copy of the signed Declaration directly to the Examiner, however all faxed correspondence for entry into the application must be directed to the central office fax at 703-872-9306. Applicant is invited to submit the signed oath to the central fax, or to include it with the

next Response. Because an Action in this Application is due immediately, any submitted oath will be considered in the next Action.

Specification

The amendments to remove nonsense characters from the specification were sufficient to overcome that objection.

The specification stands objected to because it is 128 pages in length but lacks pages numbered 94-99, while containing pages numbered 1-93 and 100-134. Applicant should file an amendment to the specification correcting the page numbering. At page 15 of the response filed 8/13/04, Applicant indicates that "the missing pages" were enclosed. This attachment was not found by the PTO. Applicant is advised that such a submission would be carefully considered for the presence of new matter and objected to if necessary.

Claim Objections

The objection to claim 12 is overcome by Applicant's amendment.

Claim 7 is objected to because it has been changed to recite "lipofectin", whereas it previously recited "lipofection". 37 CFR 1.121, paragraph (c)(2) requires that markings be provided in claims to show the addition or deletion of subject matter.

Claim 21 is objected to because it is not supported by the specification. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Claim 21 is a product by process claim drawn to the composition of claim 12 wherein "said Sertoli cells" are obtained from a

transgenic non-human animal, or its descendant, that has had DNA introduced at an embryonic state such that Sertoli cells express a biologically active moiety in a pharmacologically effective amount in vivo. Claim 12 is drawn to a composition comprising Sertoli cells that were genetically modified in a laboratory apparatus such that it expresses another biologically active moiety in a pharmacologically effective amount in vivo. So, Claim 21 is interpreted as being drawn to a composition comprising Sertoli cells that:

1) were isolated from a transgenic non-human animal that had DNA introduced at an embryonic state such that its Sertoli cells express a biologically active moiety in a pharmacologically effective amount, or from a descendent of the animal, and

2) were subsequently modified in a laboratory apparatus such that it expressed another biologically active moiety in a pharmacologically effective amount in vivo.

The specification does not support this process of making doubly modified Sertoli cells. Note that a Sertoli cell isolated from the transgenic non-human animal, without further modification, was never genetically modified in a laboratory apparatus as required by claim 12, because the genetic modification giving rise to the animal occurred at the embryonic state, and the specification does not contemplate identification and isolation of Sertoli cells from an embryo. Instead, the specification teaches at page 38, lines 18 and 19 that "transgenic animals are produced by transfections of the germ cells (usually oocytes) rather than the somatic cells that are

the targets of gene therapy efforts." Because Sertoli cells are somatic cells, it follows that the specification does not support making a transgenic animal by modification of a Sertoli cell, and does not support a transgenic animal of claim 21 comprising cells of claim 12. Instead the transgenic animal must serve as the source of the cells that are used in the process described in claim 12. As noted above, this entire process is not supported in the specification.

The Examiner believes that Applicant may have intended to claim a composition comprising Sertoli cells isolated from a transgenic non-human animal, or its descendents, wherein the transgenic animal was made by introduction into embryonic cells of DNA allowing expression of a biologically active moiety in Sertoli cells, and wherein the Sertoli cells of the composition express the biologically active moiety at amounts that are pharmacologically effective in vivo. If this is true, then an amendment to that effect is suggested.

Claim 24 is objected to because "neurotansmitters" is misspelled.

Rejections Withdrawn

The previous rejections of claims 1, 7-13, 15-18, 21, 22, and 24 for indefiniteness are withdrawn in view of Applicant's amendments. At page 16 of the response Applicant indicates that claims 7 and 8 were canceled. However, these claims remain in Applicant's listing of the claims, and were amended in the response, so the Office has not canceled them. Claims 7 and 9 are newly rejected under this statute in this Action.

Applicants amendments would have been sufficient to overcome the rejection of claims 1, 7-13, 15-18, 21, 22, and 24 for lack of adequate enablement. However, after further consideration, new grounds of rejection under 35 USC 112, first paragraph are set forth below.

The rejection of claims 1, 8, 9, 11-13, 15, and 20-22 under 35 U.S.C. 102(b) as being anticipated by Culver et al (Proc. Nat. Acad. Sci. USA 88, 3155, 1991) is withdrawn in view of Applicant's amendment deleting cells of the immune system.

The rejection of claims 1 and 7 under 35 U.S.C. 102(b) as being anticipated by Builder et al (US Patent 5,451,660, issued 9/19/95) is withdrawn in view of Applicant's amendment requiring administration to a patient.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 contains the trademark/trade name "lipofectin". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any

particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a nonviral physical method of genetic modification and, accordingly, the identification/description is indefinite. Also the claim is indefinite because "lipofectin" is not a method, as required by the claim, instead it is a product. This claim previously recited "lipofection" rather than "lipofectin". It is recommended that "lipofection" should be re-substituted for "lipofectin".

Claim 9 is indefinite because it is unclear whether the scope of "infusions" is intended to be limited to intravenous, intramuscular, intraperitoneal, and subcutaneous infusions, or whether Applicant intends to embrace any and all infusions.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in

the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 7 as currently written contains the term "lipofectin" which is not supported in the specification. As noted above, claim 7 originally recited "lipofection" rather than "lipofectin".

Scope of Enablement

Claims 1, 7-13, 15-18, 20-22, and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of providing a pharmacologically effective amount of a neurotrophin in vivo by implanting into the central nervous system of an individual Sertoli cells that have been isolated and modified in a laboratory apparatus so as to express and secrete said neurotrophin, does not reasonably provide enablement for methods of providing pharmacologically effective amounts of other biological moieties, as broadly claimed, that are expressed by Sertoli cells as a result of genetic modification. Neither is the specification enabled for methods of providing a pharmacologically effective amount of a neurotrophin in vivo by implanting into the central nervous system of an individual Sertoli cells that express, but do not secrete neurotrophin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. With regard to claims 12 and 21, the specification is not enabling for transgenic animals that have had DNA introduced at an embryonic state such that Sertoli cells of the animal express a biologically active

moiety in a pharmacologically effective amount. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

Claims 1 and 7-11 embrace methods of providing a biologically active moiety in vivo in pharmacologically active amounts by administering Sertoli cells to a patient, wherein the Sertoli cells are naturally immune privileged and have been genetically modified to produce the biologically active moiety. Claims 12-18, 20-22, and 24, are drawn to compositions comprising Sertoli cells that have been genetically modified to express a biologically active moiety in an amount that is pharmacologically active in vivo. In view of the teachings of the specification as a whole, the intended use of these compositions is the delivery of pharmacologically active amounts of compounds to individuals in vivo. As discussed above, a "pharmacologically effective amount" is interpreted as an amount that allows the prevention, diagnosis, alleviation, treatment, or cure of a disease in an animal to which the substance is administered.

The elected biologically active moiety is a neurotrophin. The specification also teaches a variety of other biologically active moieties for delivery, including e.g. insulin for the treatment of diabetes, as well as gangliosides. See page 30, line 21, and claim 23.

Essentially, Applicant views the invention as an improvement that overcomes problems associated with ex vivo gene therapy by allowing sustained, systemic delivery

of proteins and peptides in vivo with little or no need for chronic immunosuppression, due to the immune-privileged status of Sertoli cells.

State of the prior art

Use of Sertoli cells in therapy

The prior art taught that Sertoli cells could be transplanted to provide immunologically privileged sites to support cells intended to treat disorders such as diabetes. For example, Selawry et al (US Patent 5,725,854, issued 3/10/98) taught a method of treating a disease that results from a deficiency of a biological factor in a mammal wherein said method comprises administering human, bovine, or porcine Sertoli cells and a therapeutically effective amount of cells that produce said biological factor to a mammal, wherein said Sertoli cells are administered in an amount effective to create an immunologically privileged site. See claim 1.

The prior art also taught that unmodified Sertoli cells could be used to treat Parkinson's disease. For example Sanberg et al (US Patent 5,702,700, issued 3/13/95) taught a method of generating in situ trophic factors for ameliorating behavioral deficits caused by Parkinson's Disease by transplanting Sertoli cells utilizing stereotaxic delivery into the brain of an adult mammal who suffers from Parkinson's Disease. See claim 1. This effect is thought to be due to the natural secretion by Sertoli cells of a variety of trophic factors that aid in neural growth and regeneration. See e.g. Table 1 at column 5 of Sanberg.

Ex vivo gene therapy in general

At page 14, the specification lists major problems in the field of gene therapy at the time of the invention including:

1) inability to achieve efficient gene transfer;

2) lack of persistence in gene maintenance and expression;

3) inability to achieve expression in appropriate tissues and cells;

4) immunorejection after introduction of genetically modified allogeneic or xenogeneic cells;

5) inadequate understanding of the interactions of the vectors with the host, and

6) lack of understanding of the results of gene therapy protocols, which are hindered by a low frequency of gene transfer, reliance on qualitative assessments of transfer and expression, lack of suitable controls and rigorously defined endpoints.

Orkin and Motulsky (1995) taught that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). These authors also taught that problems exist achieving the appropriate level of expression within cells or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) taught, regarding gene therapy in general, that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). With respect to ex vivo

gene therapy, Verma taught that gene silencing was a problem, that one solution was related to obtaining the appropriate enhancer/promoter combination, but that the search for appropriate enhancer/promoter combinations was a case of trial and error for a given type of cell. See page 240, columns 2 and 3. Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). More recently, Romano et al (Stem Cells 18:19-39, 2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and appropriate expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. While the instant invention is largely directed to the issue of immune response against genetically modified, implanted cells, it fails to adequately address issues of the amount and control of expression required for particular gene products, and how to obtain and maintain that control.

Specific cases of ex vivo gene therapy relevant to recited embodiments

The instant disclosure contemplates treatment of neurological damage by delivery of neurotrophin-secreting Sertoli cells. A variety of publications shows that neurotrophins are secreted factors that can be used to treat neuronal damage by ex

vivo methods. For example, cells can be genetically modified to secrete pharmacologically effective amounts of neurotrophins in vivo, and damage to the CNS can be treated by implantation of such cells. See e.g. Arenas et al (Nature, (1994 Jan 27) 367 (6461) 368-71), Ebendal et al (Journal of Neurology, (1994 Dec) 242 (1 Suppl 1) S5-7), and Martinez-Serrano et al (Journal of Neuroscience (1996 Aug 1) 16 (15) 4604-16) who teach the use of genetically modified cells including fibroblasts, immortalized skeletal muscle cells, and neural stem cells, respectively to secrete neurotrophins in vivo. Also, Gage et al (US Patent 5,082,670, issued 1/21/92) taught a method for treating defective, diseased or damaged cells in the mammalian central nervous system comprising grafting a donor cell from the same mammalian species into the central nervous system, said donor cells genetically modified to produce a functional molecule in a sufficient amount to ameliorate said defective, diseased or damaged cells in the central nervous system. See claim 1.

The instant disclosure contemplates the treatment of diabetes by delivery of insulin-secreting Sertoli cells. It was recognized in the prior art that such treatment would depend on being able to duplicate the regulated insulin secretion of pancreatic beta cells. Tiedge et al (Exp. Clin. Endocrinol. Diabetes 103 Suppl. 2: 46-55, 1995) taught that this would require obtaining cells that expressed the appropriate proteases to process preproinsulin to insulin, and that contained a glucose sensing apparatus comprising the appropriate ratio of low affinity GLUT-2 glucose transporter to high affinity GLUT-1 glucose transporter, and an appropriate ratio of the low affinity glucokinase to high affinity hexokinase. See lines page 47, 20-31 of paragraph

bridging pages 47 and 48; page 48, column 1, lines 2-48. Shortly after the time of the invention, Mitanchez et al (Endocrine reviews 18(4): 520-540, 8/1997) concurred that insulin-expressing cells for diabetes treatment must contain: a glucose sensing apparatus, low expression of hexokinase relative to glucokinase, efficient processing of proinsulin to insulin, and efficient regulation of insulin secretion in response to glucose. Mitanchez states that "no beta-cell surrogate endowed with all these characteristics exists." See page 531 column 2, second and third full paragraphs. Dong et al (Current Gene Therapy 2:403-414, 2002) evaluated treatment of diabetes with engineered cells and stated that "attempts to achieve adequately regulated insulin production are stymied by the lack of appropriate surrogate cells that are able to detect blood glucose variations and release insulin in a glucose-dependent manner." So it is clear that those of skill in the art recognized the problem of regulated glucose expression prior to the time of the invention but, despite the availability of insulin, glucokinase, and GLUT-2 genes, and cellular engineering techniques, have not been able to overcome it since that time. In assessing attempts to engineer glucose responsiveness into non-beta cells Docherty (Clin. Sci. 92(4): 321-330, 1997) notes that "[o]bviously, components in addition to GLUT-2 and glucokinase are required to engineer glucose responsiveness into non-beta-cell lines."

Guidance and working examples in the specification

The specification teaches no working example of any method of using genetically modified, naturally immune privileged Sertoli cells to produce a pharmacologically effective amount of any biological moiety in any organism in vivo. The specification

teaches a prophetic example of the production of human growth hormone in a rat (Example 6, pages 59-61), and a prophetic example of treating spinal injury in a rat by delivery of Sertoli cells modified to express neurotrophin NT-3 (Example 9, pages 69-82). This example is supported by prior art data showing treatment of spinal cord injury by transplantation into the spinal cord of fibroblasts genetically modified to secrete neurotrophin 3 (NT-3) (see Fig. 9). The specification asserts that Sertoli cells transfected with an NT-3 expression vector and transplanted into the spinal cord express NT-3 and that culture supernatants of transfected Sertoli cells contained sufficient NT-3 to cause neurite outgrowth in an in vitro assay (page 79, lines 18-29).

Guidance in the specification with regard to rendering a cell glucose responsive for appropriate insulin production is limited to two sentences at page 32, lines 19-23 in which the specification indicates that one could modify a cell with a glucose transporter and an insulin gene with glucose response elements. However, the instant specification fails to account for proper processing and secretion of insulin, and provides no guidance specific to Sertoli cells as to how obtain the complex glucose responsiveness required to treat diabetes as discussed above. Mitanchez (1997) showed that proper glucose sensing requires more than just expression of a glucose transporter, it also requires the proper ratio of glucokinase to hexokinase. See paragraph bridging pages 531 and 53. The specification provides no guidance as to how to obtain this ratio in Sertoli cells.

The specification also considers a variety of other biologically active moieties for delivery in pharmacologically active amounts, including gangliosides, leptin, and clotting

factors II, VII, and X, but provides no guidance whatsoever as to how much of these compounds is required for a pharmacological effect, or how to modulate expression gene expression in order to obtain such an effect. For example, with regard to the expression of a pharmacologically effective amount of gangliosides, it is noted that gangliosides are lipids, not gene products. The specification provides no guidance whatsoever as to what is a pharmacologically effective amount of a ganglioside, or how to genetically modify a Sertoli cell to express that amount. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the process of modifying a cell to produce and secrete insulin in a glucose-responsive manner, the disclosure of amount of a ganglioside or other factor that is pharmacologically effective, the process of modifying a Sertoli cell to produce

that amount of a ganglioside or factor, and disclosure of the purpose for which it is effective, and are not minor details that can be overlooked in the process of providing an enabling disclosure, particularly in view of the unpredictability in the art. MPEP 608.01(p) speaks to the issue of the completeness of the specification for the practice of a claimed invention, stating, "While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention." In this case, the invention addresses only the aspect of immune response in gene therapy without addressing art recognized problems with gene expression.

In view of the breadth of the claims with regard to the unlimited scope of pharmacologically effective molecules and pharmacological effects embraced, the state of the prior art of obtaining pharmacological delivery of insulin specifically and gene therapeutics in general, the failure to provide guidance where the prior art indicates unpredictability of obtaining pharmacologically relevant gene expression, and the complete failure to provide any guidance whatsoever regarding a variety of contemplated pharmacological agents such as gangliosides, one of skill in the art would have to perform undue experimentation in order to make the claimed products and use the claimed methods commensurate in scope with the claims. With regard to claim language requiring only expression, but not secretion of biologically active moieties, because neurotrophins are secreted factors that act by binding to cell membrane

receptors, one of skill in the art could not use neurotrophin expressing cells for pharmacological effect in vivo unless the cells also secreted the neurotrophins.

The remainder of the rejection applies to claims 12 and 21.

Nature of the invention and breadth of the claims

Claim 21 depends from claim 12 and is drawn to a composition comprising Sertoli cells from a non-human transgenic animal, or its descendant, wherein the transgenic non-human animal has had DNA introduced at an embryonic state such that said Sertoli cells express a biologically active moiety in a pharmacologically effective amount. The claim is not limited as to the nature of the pharmacologically effective biological moiety, the nature of the pharmacological effect, or the type of Sertoli cell-containing animal. The phrase "pharmacologically effective amount" is not defined in the specification. According to Steadman's Medical Dictionary (26th Edition, 1995) "pharmacology" as the science concerned with drugs, their sources, appearance, chemistry, actions, and uses, and is concerned with the biochemical mechanisms responsible for the actions of drugs, the pharmacology of therapeutic agents in the prevention, treatment, and control of disease in humans. Its objective is to find and develop new therapeutic agents. In the same dictionary, "drug" is defined as a "therapeutic agent; any substance, other than food, used in the prevention, diagnosis, alleviation, treatment, or cure of disease in man and animal." Thus, a "pharmacologically effective amount" is interpreted as an amount that allows the

prevention, diagnosis, alleviation, treatment, or cure of a disease in an animal to which the substance is administered.

Guidance and working examples in the specification

The specification provides a prophetic example of a making a transgenic rat in which human growth hormone is produced in Sertoli cells using a Sertoli rat androgen binding promoter. No working example is disclosed.

State of the art and level of predictability

It was well known in the art at the time of the invention that the production of transgenic animals with desired characteristics was highly unpredictable. As of the effective filing date of the claimed invention only a limited number of species of transgenic animals had been produced. There is no evidence to support the position that transgenic animals from all species possessing the desired phenotype can be readily produced without undue experimentation. It was also well known in the art that the expression of a transgene and the effects of its expression on the animal as a whole are not predictable due to numerous uncontrollable factors such as the site of integration and methylation-inactivation of the transgene. For example, Ebert et al (Mol. Endocrinol. 2(3) : 277-283, 1988) disclose the production of transgenic mice expressing human somatotropin regulated by the mouse metallothionein promoter at levels sufficient to cause an increase in growth; however, expression of the same transgene in pigs did not produce pigs exhibiting the same phenotypic result (page 277, Introduction, column 2). Furthermore, Hammer et al (J. Anim. Sci. 63 : 269-278, 1986), disclose the production of transgenic mice, sheep and pigs; however only mice exhibited an increase

in growth due to the expression of human growth hormone (pages 276-277, Subsection: (Effect of Foreign GH on Growth).

Wall (Theriogenology 45: 57-68, 1996) disclosed the unpredictability of transgene behavior was due to factors such as position effect and unidentified control elements that may result in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Additionally, Kappel et al (Curr. Opin. Biotech. 3 : 548-553, 1992) disclosed the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, 3rd full paragraph). Mullins et al (J. Clin. Invest. (1996) 98(11), Supplement S37-S40) taught that a given construct may react very differently from one animal to another due to position effects that can cause loss of cell specificity of expression, overexpression, or silencing of the transgene. See page S37, lines 7-12, and page S39, first sentence of first paragraph.

While it is within the skill of the art to produce a mouse with almost any gene integrated into the genome, the resulting expression and phenotype remains unpredictable and often elusive. It is not within the skill of the art to create an animal of any species with successful integration to predictably obtain the desired expression and phenotype. The specification does not provide sufficient direction or example to enable one of skill in the art to create transgenic animals that predictably express a transgene at a pharmacologically effective level. The amount of experimentation required to obtain a desired amount of expression in a transgenic animal is very high relative to that required for transfecting cultured cells and selecting for expression levels in vitro.

In view of the breadth of the claims, embracing pharmacologically effective expression of any transgene in any Sertoli cell-containing animal, the unpredictable state of the art as set forth above, the lack of any working example in the specification, and the lack of adequate guidance regarding predictably obtaining pharmacologically effective transgene expression, one of skill in the art would have to perform undue experimentation in order to make the recited transgenic animals.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12, 13, 15, 18, 20-22 and 24 stand rejected under 35 U.S.C. 102(b) as being anticipated by Builder et al (US Patent 5,451,660, issued 9/19/95).

Claim 12 is drawn to a composition comprising Sertoli cells that are naturally immune privileged and that have been isolated and genetically modified in a laboratory apparatus to express a biologically active moiety such that said cells express said biologically active moiety in a pharmacologically effective amount in vivo.

Builder taught methods of genetically modifying Sertoli cells to express neurotrophins. See column 7, lines 49 and 50; column 8, lines 7-10; column 9, lines 63-66; and column 12, lines 37, 43, and 54-59. Absent evidence to the contrary the cells of Builder express the neurotrophin in an amount that would be pharmacologically

effective in vivo. With regard to claim 22, the property of being adherent is an inherent property of Sertoli cells. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Response to Arguments

Applicant's arguments filed 8/13/04 have been fully considered but they are not persuasive.

Applicant argues at page 18, paragraph 4 of the response that Builder neither discloses nor suggests the use of Sertoli cells in vivo, and cannot anticipate the claims for lacking these limitations. However, the rejected claims are not method claims, instead they are drawn to compositions with an intended in vivo use. As stated above, absent evidence to the contrary, the cells of Builder are enabled for the intended use because they are structurally indistinguishable from the claimed cells. Applicant has not pointed to any structural difference between the claimed cells and those of Builder, and

has not explained why the cells of Builder could not be used as intended in the rejected claims. For these reasons the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12 ,16, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Builder et al (US Patent 5,451,660, issued 9/19/95) in view of Lipshultz et al (J. Clin. Endocrin. Metab. 55(2): 228-237, 1982).

Claim 16 is drawn to a composition comprising human Sertoli cells that are naturally immune privileged and that have been isolated and genetically modified in a laboratory apparatus to express a biologically active moiety such that said cells express said biologically active moiety in a pharmacologically effective amount in vivo.

Builder taught methods of genetically modifying cells to express neurotrophins, and exemplified the mouse Sertoli cell line TM-4. See column 7, lines 49 and 50; column 8, lines 7-10; column 9, lines 63-66; and column 12, lines 37, 43, and 54-59. Regarding cells that could be used in the invention, Builder stated "any higher eukaryotic cell culture is suitable," see sentence bridging columns 11 and 12.

Builder did not teach the use of human Sertoli cells or primary Sertoli cells.

Lipshultz taught the isolation and culture of primary human Sertoli cells. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the cells of Lipshultz in the invention of Builder. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). In this case, Builder stated that any higher eukaryotic cell culture is suitable for use in the invention, and specifically mentioned a mouse Sertoli cell line, as well as several human cell lines, e.g. human embryonic kidney cells, human cervical carcinoma cells, human lung cells, and human liver cells. See column 7, lines 37-53. Clearly Sertoli cells were considered to be acceptable cells by Builder, there was no general requirement for mouse cells, and a variety of human cells was acceptable. The human primary Sertoli cells of Lipshultz are equivalents to the mouse Sertoli cells of Builder inasmuch as they are clearly a higher eukaryotic cell culture. Absent evidence to the contrary, the human cells of Lipshultz would function in the invention of Builder, and a prima facie case of obviousness exists.

Claims 12 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Builder et al (US Patent 5,451,660, issued 9/19/95) in view of Guillou et al (J. Biol. Chem. 266(15): 9876-9884, 1991).

Claim 17 is drawn to a composition comprising primary Sertoli cells that are naturally immune privileged and that have been isolated and genetically modified in a laboratory apparatus to express a biologically active moiety such that said cells express said biologically active moiety in a pharmacologically effective amount in vivo.

Builder taught methods of genetically a modifying mouse Sertoli cell line to express neurotrophins. See column 7, lines 49 and 50; column 8, lines 7-10; column 9, lines 63-66; and column 12, lines 37, 43, and 54-59.

Builder did not teach the use of primary Sertoli cells.

Guillou studied Sertoli cell-specific expression of the human transferrin gene in primary cultured rat Sertoli cells. Reporter constructs were constructed comprising various regions of the 5' flanking regions of the human transferrin gene, operably linked to a chloramphenicol acetyltransferase CAT reporter gene, and CAT activity in transfected cells was measured

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the primary Sertoli cells of Guillou for the Sertoli cells of Builder. One of ordinary skill in the art would see these cells as a equivalents for the purpose of producing a heterologous gene product because they can clearly both be transfected to produce a gene product. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining

essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). Builder stated that any higher eukaryotic cell culture is suitable for use in the invention. See column 7, lines 37-53. In this case both mouse and rat cells have the essential function of expressing transfected genes, and would be considered equivalents. Absent evidence to the contrary, the primary cells of Guillou would function in the invention of Builder, and a prima facie case of obviousness exists.

Conclusion

No claim is allowed. Claims 1 and 7-11 are free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax

number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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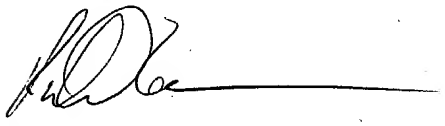

Richard Schnizer, Ph.D.